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Impact of discontinuing tremor suppressing medications following thalamic deep brain stimulation

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ABSTRACT

Background: Many essential tremor patients continue to require tremor suppressing medications following deep brain stimulation. The true incidence of medication usage in the years following surgery remains unclear, and the use of medications has not been included in the post-operative analyses of tremor severity and also quality of life.

Methods: Among 28 essential tremor patients treated with deep brain stimulation at a single center between January 2002 and April 2010, we analyzed the prevalence and dosage of pre-operative tremor suppressing medications versus post-operative medications at 12 and 36 months following surgery. We also assessed the influence of medication continuation on clinical outcome measures, such as the Fahn-Tolosa-Marin Tremor Rating Scale, and the 36 item short-form health quality of life survey.

Results: Both unilateral and bilateral deep brain stimulation resulted in a decrease in primidone use ($p = 0.0082$, 0.046, respectively), and bilateral deep brain stimulation patients used less tremor suppressing medications 36 months following surgery ($p = 0.02$). The decision to discontinue primidone after surgery resulted in a non-significant long-term improvement in tremor motor score (23 points versus 15 points, $p = 0.19$), and did not significantly influence the physical and mental composite quality of life scores ($p = 0.81$, 0.23, respectively).

Conclusions: Bilateral deep brain stimulation effectively eliminated the need for tremor suppressing medications, while unilateral stimulation was not as effective in reducing medication usage. Clinicians and patients should be aware that discontinuation of primidone after surgery may worsen tremor in unilateral deep brain stimulation cases, but discontinuation will not likely impact quality of life.

1. Introduction

Essential tremor (ET) is a common movement disorder that can result in significant functional disability particularly in severe cases [1,2]. ET is usually slowly progressive with a variable clinical course, as well as a variable response to medical treatments [3–7]. There are many pharmacological treatments for ET, however few effectively control moderate to severe tremor, especially as the disease progresses [1,2]. Ventralis intermedius nucleus deep brain stimulation (DBS) has been proven to be an effective surgical treatment for select patients who are refractory to standard pharmacologic treatment [8–10].

Many patients may continue to require medications after DBS in order to achieve effective tremor control. This issue has not been well studied, but one small study has recently suggested that the use of tremor suppressing medications may not change after intervention with DBS, however there was a non-significant dose reduction observed [11]. Still, another small study reported that the majority of patients discontinue medications within the first year following unilateral DBS surgery, and the in the remaining patients post-DBS medication usage consists of beta-blocker use for other cardiac indications [12]. The true incidence of tremor suppressing medication usage in the years following DBS remains unclear. Further, prior studies have failed to correlate the continuation of tremor suppressing medication following DBS with clinical tremor scales or with quality of life measures.

In this retrospective study, we sought to extract and to utilize long-term data from the UF-INFORM database. We have aimed to dissect the issue of medication usage before and after ventralis intermedius nucleus DBS by analyzing the prevalence and dosage of pre-operative tremor suppressing medications versus post-

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operative medications at 12 and 36 months following DBS. We hypothesized that all ET patients would decrease the use of tremor suppressing medications after DBS, but that the decrease would be more dramatic among those receiving bilateral stimulation. We further aimed to expose a potential relationship between continued medication usage and relevant clinical outcome measures. We hypothesized that there would be a relationship between continued primidone use, tremor severity, and quality of life.

2. Methods

2.1. Study population

An IRB approved UF-INFORM database search of all ET patients treated with ventralis intermedius nucleus DBS surgery between January 2002 and April 2010 was performed. Inclusion was dependent upon the availability of demographic features, baseline Fahn–Tolosa–Marin Tremor Rating Scale (TRS) scores, and the presence of clinical follow-up of at least 36 months.

General characteristics of the cohort were noted. Age, sex, duration of ET symptoms, DBS target coordinates, DBS trajectory angles, and pre-operative history of psychiatric disorders were recorded. Tremor control medications were recorded at each visit. MOS 36 item short-form health quality of life survey (SF-36), Patient Global Impression Scale (PGIS), and Clinical Global Impression Scale (CGIS) were also noted at baseline and follow-up examinations. TRS (total and subscores) was noted at the baseline examination (pre-DBS) as well as at follow-up examinations (12 and 36 months). Laterality of lead placement was recorded for all subjects. Comparisons were performed between baseline characteristics of unilateral and bilateral subjects, and all outcome analyses were performed separately for unilateral and bilateral subjects.

A total of 69 ET patients received ventralis intermedius nucleus DBS surgery at the UF Center for Movement Disorders & Neurorestoration between January 2002 and April 2010. Ten subjects were excluded from analysis because they received prior DBS surgery at an outside facility. An additional 4 subjects were excluded because the stimulator was revised in a second procedure. Twenty-four subjects were excluded because they did not have a follow-up examination performed at 36 months (13 subjects lost to follow-up and 11 subjects were operated on less than 36 months prior). One subject was excluded because the DBS target was changed to STN, and two subjects were excluded because the DBS batteries were not placed following lead insertion (Supplementary Fig. 1).

2.2. Medications

Tremor suppressing medications, including dosages, were abstracted from patient charts at the pre-DBS evaluation and each follow-up evaluation (12 and 36 months). Primidone, beta-blockers, and benzodiazepines were the focus of the medication analysis. The medical indication was confirmed in each case, and only those used for tremor control were included in the final analysis.

2.3. Fahn–Tolosa–Marin Tremor Rating Scale

Fahn–Tolosa–Marin TRS motor and ADL scores were recorded at baseline (pre-DBS) and each follow-up examination. The TRS motor score includes the Fahn-Tolosa-Marin TRS questions 1–14 (parts A and B), addressing tremor severity, location, and function in drawing and pouring. The TRS ADL score includes question 15–21, addressing speaking, feeding, hygiene, dressing, writing, and working. Each question receives a score between 0 and 4 (maximum possible TRS motor score is 116; maximum possible TRS ADL score is 28). At all follow-up examinations, TRS scores were recorded in both the ON and OFF stimulation states (off stimulation condition evaluation always followed the on condition after an off period of 30 min—patients and examiners not blinded). At each examination, a single assessor assigned all TRS scores. The same assessor did not reassess every patient at each follow-up examination. All examiners at the UF Movement Disorder Center were trained by a Movement Disorder's specialist and the Fahn–Tolosa–Marin TRS has been demonstrated to maintain good inter-rater reliability [13].

2.4. Short form (36) health survey

The 36 item short-form health quality of life survey (SF-36) is a standardized quality of life assessment divided in eight dimensions of health: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health [14]. The questions within each dimension are totaled to receive a score between 0 and 100. Dimensions are further grouped to generate a physical composite score (PCS) and mental composite score (MCS). A linear *T* score transformation is applied to these composite scores to allow for normative based scoring in which the US national average is 50 (per 1998 National Survery of Functional Health Status) with a standard deviation of 10 [15]. The SF-36 was completed by patients at the baseline (pre-DBS) examination and at each of follow-up examination.

2.5. Statistical analysis

The primary outcome measures were (1) tremor control medication usage at 12 months post-DBS and (2) at 36 months post-DBS. Initially, the Chi-squared test was employed to compare medication use between unilateral and bilateral patients. Subsequently, change in medication use following DBS was assessed in a paired fashion with the McNemar test. Secondary outcome measures include (1) TRS motor and ADL scores and (2) SF-36 score 12 and 36 months following DBS surgery. Given the ordinal nature of TRS scoring system, the Wilcoxon–Mann–Whitney test was employed to analyze the influence of primidone use on tremor severity and ADL score, and given the normative nature of the SF-36 composite scores, *t* tests were used to compare quality of life outcome measures.

In order to confirm the efficacy of DBS stimulation, TRS scores were recorded while ON and OFF stimulation at each follow-up examination. The Wilcoxon signed-ranks test was employed to compare on-stimulation and off-stimulation scores in a paired fashion at each follow-up examination. In order to confirm the continued benefit of stimulation over time, the Wilcoxon signed-ranks test was used to compare on-stimulation scores at each evaluation throughout the follow-up period. Again, all analyses were performed separately for unilateral and bilateral patients.

All statistical analyses were performed with Stata/SE 10.0 (StataCorp, College Station, TX).

3. Results

Twenty-eight subjects that received ventralis intermedius nucleus DBS met inclusion criteria and remained in the final cohort. Excluded patients were similar to subjects in the final cohort with respect to all demographic features, baseline tremor severity, and surgical characteristics, but excluded subjects experienced fewer years of symptoms as compared to those included in the final cohort. Of the 28 subjects in the final cohort, 19 received placement of DBS leads unilaterally, while 9 subjects received bilateral leads. Those who received unilateral surgery did not differ from those who received bilateral surgery, with respect to demographic features, surgical details, and baseline clinical performance (Table 1).

Tremor suppressing medications and dosages were recorded at all evaluations (before and after DBS). In comparing unilateral and bilateral patients, medication usage was similar at baseline and 12 months, but at 36 months, a smaller proportion of bilateral patients used tremor suppressing medications ($p = 0.02$) (Supplementary Table 1b). Subsequently, as medication usage was compared before and after DBS, unilateral and bilateral patients were assessed separately (Table 2). In the unilateral group, a decrease in overall medication use was noted at 12 months, but that decrease was no longer observed at 36 months. Analysis of specific medications

Table 1
Cohort baseline characteristics.

	Unilateral ($n = 19$)	Bilateral ($n = 9$)	p value
Age, years	71 (13.0)	75 (3.6)	0.33
Sex[a]	13 (68)	5 (56)	0.51
Right handed[a]	18 (95)	9 (100)	0.48
Symptom duration, years	38 (20.4)	32 (21.0)	0.52
Left sided lead placement[a]	16 (84)	9 (100)	0.21
Baseline TRS motor score	40 (9.6)	36 (13.7)	0.43
Baseline TRS ADL score	18 (4.9)	16 (6.3)	0.40
SF-36 PCS T score	46 (11.8)	40 (10.4)	0.32
SF-36 MCS T score	51 (10.3)	44 (9.3)	0.16
x target, mm	−8.8 (10.7)	−13.9 (1.5)	0.07
y target, mm	−5.9 (1.6)	−6.5 (1.2)	0.12
z target, mm	−1.6 (1.9)	−2.0 (1.8)	0.39
AC-PC angle, degrees	59.9 (4.3)	63.2 (5.0)	0.22
Centerline angle, degrees	7.6 (6.3)	5.1 (6.1)	0.28

All values are reported as mean (SD) unless otherwise noted.
Comparisons performed with *t*-test for continuous variables, Willcoxon–Mann–Whitney test for ordinal variables, and chi-squared test for dichotomous variables.
x, *y*, *z* target refers to the Cartesian location of distal lead tip.
AC-PC angle refers to the angle relative to the sagittal plane.
Centerline angle refers to the angle relative to the coronal plane.
[a] values are reported as *n* (%).